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DOCKET #: 271010-211

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent Examining Operations

Applicant(s): KOHN, *ET AL.*

Serial No: 08/225,478 Art Unit: 1804

Filed: APRIL 8, 1994 Examiner: MILNE

Title: GENE THERAPY BY ADMINISTRATION OF GENETICALLY ENGINEERED CD34+ CELLS OBTAINED FROM CORD BLOOD

TRANSMITTAL LETTER

Assistant Commissioner for Patents
Washington, D.C. 20231

SIR:

Enclosed please find the following:

1. Response to Office Action dated June 7, 1996;

2. Request for two (2) month extension of time;

3. Check No. 23946 in the amount of $390.00; and

4. A self-addressed, postage paid postcard, date stamp and return of which is respectfully requested.

The Commissioner is authorized to charge payment of any additional filing fees required under 37 CFR 1.16 associated with this communication or credit any overpayment to Deposit **Account No. 03-0678.**

FIRST CLASS CERTIFICATE

I hereby certify that this correspondence is being deposited today with the U.S. Postal Service as First Class Mail in an envelope addressed to:

Assistant Commissioner for Patents
Washington, D.C. 20231

Raymond J. Lillie 11/5/96
Raymond J. Lillie, Esq. **Date**

Respectfully submitted,

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Claims 1-26 are currently pending in U.S. Patent Application Number 08/225,478. Applicants' amendment filed 4-22-96 has been carefully considered and incorporated into the record of the instant application.

Any rejection not reiterated in this office action is hereby considered withdrawn in light of the amendment filed 4-22-96.

The speicification remains objected to under 35 U.S.C. 112, first paragraph as failing to provide an enabling disclosure. Briefly, it was held in the previous action that in light of the high amount of unpredictability in the art and the lack of sufficient guidance in the specification regarding the invention as claimed, that it would require one of skill in the art to undertake undue experimentation in practicing the instantly claimed invention.

Applicants' intend that the instant specification discloses specific therapeutic effects that can be achieved in practicing the instant invention.

Applicants' further intend that there has been no evidence presented documenting that the administration of $CD34^{+}$ cells obtained from cord blood that are genetically engineered with at least one nucleic acid sequence encoding a therapeutic agent would not result in sustained therapeutic effects for a term

longer than that demonstrated by Applicants.

The first action based the rejection under 35 U.S.C. 112, first paragraph on the amount of unpredictability in the art that has yet to be overcome. However, to more specifically describe what was intended by a lack of predictability in the art of gene therapy, Marshall states that "there has been no unambiguous evidence that genetic treatment has produced therapeutic benefits" (p. 1050, col. 1) and that "difficulties in getting genes transferred efficiently to target cells - and getting them expressed - remain a nagging problem for the entire field" (p. 1054, col. 3). James Wilson, one skilled in the art, saying that " '{t}he actual vectors - how we're going to practice our trade - haven't been discovered yet" (p. 1055, col. 2). The Kohn reference was further cited to support the lack of predictability in the art of gene therapy as it applies to genetically altered cells as well as the conditions that said cells are cultured in.

Applicants' have not disclosed sufficient guidance regarding how to use the claimed invention a treat a human patient or provide a therapeutic effect to a human patient in a manner that would be considered predictable by those of skill in the art.

More specifically, in response to Applicants' indication on page 7 of the amendment that the Examiner admits that there are immediate therapeutic benefits, such as the development of normal numbers of T lymphocytes, normal PHA responses, and normalized

levels of deoxyadenosine metabolites, these were comments reiterating information that had been documented in the specification; however in a more just response, it does not appear as though these effects or consequences would result in methods of treatment of ADA through the transduction of $CD34^+$ cells to an infant as is claimed. Specifically, please see page 1051 of Marshall et al. which addresses this point exactly. In column 2, the reference states that:

> "Already the patients' white cell count have dropped with the initial decline in PEG-ADA doses, although the fraction of "cured T cells has increased".

There does not appear to be any evidence disclosed in the prior art or in Applicants' specification that the genetically altered CD34+ cells have themselves produced a therapeutic benefit and that the administration of PEG-ADA to the individuals, as disclosed in the working examples, is not the sole source of therapeutic results in the patients. Therefore it does not appear as though sufficient guidance has been given to the skilled artisan regarding how to use the claimed invention and achieve a therapeutic effect.

Applicants' further intend that the examiner has not met the burden in showing that cells could not be cultured in the

presence of IL-3, IL-6, and c-kit ligand transfected with at least one nucleic acid sequence encoding a therapeutic agent. However, the claims recite methods of treating an infant wherein said cells are cultured in said conditions. The issue of whether the cells can be cultured in such conditions does not pertain to the claims; rather whether a treating effect can be achieved from cells cultured in such conditions is the issue at hand. It is concluded that there is a lack of predictability in the art that would require undue experimentation in achieving such an effect.

Claims 1-24 were initially rejected under 35 U.S.C. § 103 as being unpatentable over Anderson taken with Moritz and Kohn wherein claims 1-26 were intended to be rejected for reasons of record. Applicants' response appears to indicate the understanding that all of the pending claims were rejected under the references Anderson, Moritz and Kohn therefore claims 1-26 are considered rejected over the teachings of Anderson taken with Moritz and Kohn.

Applicants' intend that Anderson in no way suggests the insertion of at least one nucleic acid sequence into $CD34^+$ cells isolated from umbilical cord blood and that said cells could be cultured and reinfused in order to achieve a therapeutic effect. Applicants' further intend that the cited prior art does not

disclose or remotely suggest that one may obtain CD34 $^{+}$ cells from cord blood, genetically engineer said cells with a therapeutic gene, and reinfuse said cells in order to achieve a therapeutic effect. These arguments are not deemed persuasive. Anderson et al disclose ADA gene therapy as a process in which a patient undergoes leukophoresis for the purpose of obtaining mononuclear cells, growing the cells in culture and transducing the T cells with a retroviral vector containing the normal ADA gene (as well as the NeoR gene), and finally reinfusing the autologous lymphocytes into said patient with the intent that the newly inserted therapeutic gene will encode adenosine deaminase *in vivo*. Moreover, Anderson discusses the concerns of transducing only mature cells and not stem cells (CD34 $^{+}$ stem cells) in the existing protocol, page 811. Therefore Anderson succeeds in providing sufficient motivation to use CD34 $^{+}$ cells for the purpose of transducing them in order to provide a therapeutic effect. Anderson teaches the manipulation of CD34+ cells and addresses the method of transducing CD34 $^{+}$ cells for the purpose of gene therapy with respect to hematopoietic stem cells such as the CD34^{+} lineage.

The deficiency of the primary reference is cured by Moritz et al. who teaches that CD34 $^{+}$ cells can be obtained from umbilical cord blood. Moritz further establishes that the cord blood cells were to be genetically engineered prior to reinfusion into a patient and that these progenitor cells had already been

shown to have the capacity to reconstitute the lympho-hematopoietic system in transplant protocols thereby establishing a substantial expectation of succeeding in the transplantation of autologous $CD34^+$ stem cells that have been genetically reengineered. Kohn further discloses the ability of those of ordinary skill in the art to culture $CD34^+$ cells, and the disclosed growth factors may enhance gene transfer efficiency.

Therefore, it is concluded that at the time the invention was made, one of ordinary skill in the art would have had both motivation to combine the references and a substantial expectation of success of obtaining $CD34^+$ cells, transducing said cells with a therapeutic gene, and reinfusing said autologous cells. The cells would most certainly have been obtained from umbilical cord blood given the fact that Moritz teaches that said blood has high levels of stem cells, and that Anderson teaches that $CD34^+$ cells are stem cells that are beneficial to use in gene therapy.

In response to Applicants' argument that the Examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgement on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include

knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. *In re McLaughlin*, 443 F.2d 1392; 170 USPQ 209 (CCPA 1971).

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication from the examiner should be directed to Andrew Milne, whose telephone number is (703) 308-4213. The examiner can normally be reached from 7:00 to 4:00 (Eastern Standard Time) Monday thru Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jacqueline Stone, can be reached at (703) 308-3153. The fax number for art unit 1804 is (703) 308-0294.

Any inquiry of a general nature or relating to the status of the application should be directed to the group receptionist